

Population and Case-Control Surveillance in the Search for Environmental Causes of Birth Defects

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Synopsis

An important national health goal is to reduce morbidity attributable to birth defects and developmental disabilities. Population-based surveillance has made notable contributions toward preventing these problems; it

is also useful in monitoring changes in their incidence and in helping to identify reproductive hazards in the environment.

The Metropolitan Atlanta Congenital Defects Program of the Centers for Disease Control is a model for such surveillance activities. Its register contains data on birth defects of all infants born in the five-county metropolitan area since 1976. Information on all major malformations discernible by physical examination is collected by the register staff. Mothers of babies with selected major malformations are interviewed at length.

The register data base permits testing of new hypotheses concerning birth defects. It has speeded an extensive study of the possible effects of military service in Vietnam on the risk of having a baby with a birth defect. In addition, because of their special skills, program staff have made contributions to genetic services and to the development of national policy on maternal serum alpha fetoprotein.

I HAVE HAD THE PRIVILEGE of working for more than a decade with the Metropolitan Atlanta Congenital Defects Program, a model developed by the Centers for Disease Control (CDC). The foundation of the program's activities has been a population-based register of infants with birth defects (1). The register's value lies in its usefulness as a foundation for many epidemiologic activities and studies. I believe that the development of additional centers of epidemiologic excellence around the world to study human reproduction could play a major role in solving problems of birth defects, mental retardation, and other childhood morbidities.

Essentials of the Register

In late 1976, the Atlanta congenital defects program began to register all infants with birth defects born to residents of metropolitan Atlanta—a five-county area with 1.7 million residents where about 25,000 infants are born each year. The registration is done by members of our staff who visit all the hospitals in the area to review the records of infants born with malformations. The visits occur at least weekly for most hospitals. Since nearly all births occur in hospitals and since nearly all infants are examined by pediatricians, we believe that we have a nearly complete registration of newborns with major malformations discernible by physical examina-

tion. The resources required for such a register exclusive of automated data processing needs and medical, epidemiologic, and statistical supervision are two data abstractors and a statistical clerk. Thus, the foundation for a center of epidemiologic excellence to study human reproduction can be established with modest resources. The activities that can be developed from this foundation of information require additional resources.

Epidemiologic Activities

The rationale for epidemiologic activities based on the registry might be epitomized by the statement that the proper study of mankind is man. In many countries, systems have been established to protect human fetuses from exposure to harmful agents by conducting various testing programs that involve tissue culture and laboratory animals. Even the best of these testing systems is not foolproof. The probability remains that human defense mechanisms will fail and that fetuses will be harmed by agents judged to be safe in animal and other testing systems.

The goal of the Atlanta program is to determine as soon as possible when the human defense mechanisms break down and why. Another goal is to identify environmental causes that have been present but undiscovered for many years. Birth defects monitoring and case-control surveillance are two activities directed at detecting

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breakdowns in the nonhuman screening programs. They are also directed at identifying etiologic agents that may have slipped through the screening of laboratory animals and those etiologic agents that may have been in our environment and never tested in laboratory animals.

Monitoring the incidence of birth defects. We register birth defects as quickly as possible, and each month we look at the incidence of some 150 kinds of birth defects, seeking to determine significant changes in incidence. Three major changes have been observed—dramatic increases in the reporting of patent ductus arteriosus and ventricular septal defects and a significant decrease in neural tube defects (anencephaly and spina bifida). We have been unable to determine the reasons for these changes (2).

Case-control surveillance. Since the early 1970's, we have sought to interview the mothers of babies with selected major malformations, seeking clues to their etiology. These interviews cover a broad spectrum of information, from purely genetic to purely environmental factors. Specifically, we have sought to examine the relationship between birth defects and the use of anticonvulsants in pregnancy.

The interviews also have enabled us to identify possible breaks in the human defense mechanisms. For example, we have identified an association between diazepam and facial clefts (3).

Testing hypotheses raised by others. Case-control surveillance also permits testing hypotheses raised by others. For example, data from the interviews have permitted us to look for a relationship between birth defects and progestational agents, Bendectin (4), fever (5), and spermicides (6). At the time of our interviews we could not anticipate that these hypotheses would be raised, but by analyzing our data, we could test these ideas.

We have been able to use exposure data collected by others to test hypotheses. For example, we have tested hypotheses about putative teratogenic environmental agents such as airport noise (7) and exposure to spray adhesives (8). The availability of the registry and the

epidemiologic and statistical expertise built around the registry permitted a prompt response to these hypotheses.

Furthermore, the registry has permitted us to respond to a new public concern—whether military service in Vietnam increased the risk of having a baby with a birth defect. Because of the registry and the epidemiologic and statistical expertise gained from maintaining it, we were in a position to design, implement, and complete a study of this issue several years sooner than if we had started it de novo. In about 2 years, we will be able to complete the largest recorded case-control study of birth defects. Seven thousand interviews have been completed, and we are entering the data analysis phase. Had we not had the registry and the skilled scientific personnel who were associated with it, this study would have required several more years.

Developing and evaluating implementation strategies. Epidemiologic expertise teamed with CDC laboratory expertise permitted CDC staff to assist in conducting a demonstration project on amniocentesis in metropolitan Atlanta and to evaluate it (9). Within a year after we began this project, nearly 50 percent of pregnant women 40 years of age and older in the Atlanta area were being tested, and the vast majority of such women were offered the test. When epidemiologists in the Birth Defects Branch investigated the use of prenatal diagnosis in selected other areas of the country, they found dramatic racial and geographic variations. Only 50 percent of the women in the United States who were offered the test agreed to have it. Women living in cities were much more likely to have the test than those living in rural areas (10).

Because of the epidemiologic and statistical expertise of the staff of the Birth Defects Branch, CDC, we were able to assist in developing the maternal serum alpha-fetoprotein policy in the United States and in designing national and local protocols for evaluating its use.

Staff members have vigorously participated in discussions about the approach that should be taken in the United States regarding periconceptional use of vitamins and the possible prevention of neural tube defects. An international group, convened in August 1982, recommended a randomized clinical trial of American women who have had a child with a neural tube defect. We have carefully considered these recommendations and written a study protocol. A feasibility study will be started in 1985.

Other findings. We can obtain from the Atlanta registry good maternal age-specific data on the incidence of Down's syndrome. Epidemiologists examined these data and the national statistics on births by maternal age over

time and made an interesting observation. Changes in reproductive habits of American women between 1960 and 1978 reduced, independent of amniocentesis, the annual number of Down's syndrome cases by 50 percent and reduced the incidence or newborn prevalence by 25 percent (11). The fact that there has been a 50 percent reduction in the most common cause of mental retardation in the United States has simply been unrecognized. No one has even stood up to take credit. Although similar declines have been noted in England, Australia, and Sweden, declines have not been noted in Northern Ireland, Italy, and Spain—where the crude newborn prevalence rates of Down's syndrome are nearly twice those in the United States (12).

Expansion of the Atlanta Registry

A quality, population-based birth defects surveillance program or registry can be the basis for etiologic and health services research of national and international public health importance. Other issues related to reproductive hazards of public health importance can also be explored by following the Atlanta model.

Developmental disabilities. There is a great deal of concern in our country and around the world about harmful effects of exposure to toxic chemicals in our environment. The most dramatic example of such harm from a reproductive standpoint is the outbreak of cerebral palsy and mental retardation that occurred in Japan in the 1950s. The outbreak was shown to have been caused by the contamination of Minamata Bay with mercury from waste produced by a chemical company. The mercury was concentrated in the food chain so that the pregnant women who ate fish received a dose of mercury that was fetotoxic. Developmental disability surveillance systems were not established around the world in response to this environmental disaster, in contrast to the birth defects monitoring systems that were established after the thalidomide problem. CDC believes that developmental disabilities should be monitored, and we are working with the State of Georgia to determine the feasibility of such surveillance of developmental disabilities in metropolitan Atlanta. When this surveillance program begins, we expect to have gained the capability and expertise to assist other States and communities in their search for toxic chemical exposures that cause developmental disabilities, and we will be able to help evaluate specific concerns about these exposures.

Population-based surveillance of developmental disabilities will also provide the basis for other important epidemiologic evaluations. It will probably serve as the best tool for evaluating the effectiveness of all the resources devoted to producing healthy children. If the

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developmental disability rate and its component rates fall, our efforts toward producing healthy children can be judged to be beneficial. If the rate or rates are increasing, then we must begin to seek the cause or causes. If such a surveillance program were in place today, we might learn that the rates of cerebral palsy are increasing because babies of very low birth weight now have a higher survival rate. Such a result would point toward a renewed search for strategies to prevent low birth weight and for ways to carry out and evaluate these prevention strategies.

For years, the President's Committee on Mental Retardation has had as a goal a 50 percent reduction in the prevalence of severe mental retardation by the year 2000. The lack of population-based surveillance for mental retardation means that the Committee has no way of knowing how well the nation is doing and, further, its members are hampered in making recommendations about the best use of resources to achieve this goal. When the Atlanta developmental disability surveillance program becomes active, it should produce information of vital importance to the Committee. Finally, the Atlanta model can be used very productively to study other adverse reproductive outcomes such as low birth weight (a common cause of infant mortality in the United States), infertility, and miscarriages.

References

1. Edmonds, L. D., et al.: Congenital malformations surveillance: two American systems. *Int J Epidemiol* 10: 247-252 (1981).
2. Oakley, G. P., Jr.: Incidence and epidemiology of birth defects. *In Genetic issues in pediatrics and obstetric practice*, edited by M. M. Kaback. Year Book Publishers, Inc., Chicago, 1981, pp. 25-43.
3. Safra, M. J., and Oakley, G. P., Jr.: Association between cleft lip with or without cleft palate and prenatal exposure to diazepam. *Lancet* No. 7933: 478-480 (1975).
4. Cordero, J. F., Oakley, G. P., Jr., Greenberg, F., and James, L. M.: Is Bendectin a teratogen? *JAMA* 245: 2307-2310 (1981).

5. Layde, P. M., Edmonds, L. D., and Erickson, J. D.: Maternal fever and neural tube defects. *Teratology* 21: 105-108 (1980).
6. Cordero, J. F., and Layde, P. M.: Vaginal spermicides, chromosomal abnormalities and limb reduction defects. *Fam Plann Perspect* 15: 1618 (1983).
7. Edmonds, L. D., Layde, P. M., and Erickson, J. D.: Airport noise and teratogenesis. *Arch Environ Health* 34: 243-247 (1979).
8. Hanson, J. W., and Oakley, G. P., Jr.: Spray adhesives and birth defects [letter]. *JAMA* 236: 1010 (1976).
9. Oakley, G. P., Jr., et al.: A community approach to prenatal diagnosis. *In Service and education in medical genetics,*

edited by I. H. Porter and E. B. Hooks. Academic Press, Inc., New York, 1979, pp. 163-182.

10. Adams, M. M., et al.: Utilization of prenatal genetic diagnosis in women 35 years of age and older in the United States, 1977 to 1978. *Am J Obstet Gynecol* 139: 673-677 (1981).
11. Adams, M. M., Erickson, J. D., Layde, P. M., and Oakley, G. P., Jr.: Down's syndrome—recent trends in the United States. *JAMA* 246: 758-760 (1981).
12. International Clearinghouse for Birth Defects Monitoring Systems: 1981 annual report. March of Dimes, White Plains, N.Y., 1983.

Facts, Projections, and Gaps Concerning Data on Aging

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Synopsis

In 1900, approximately 25 percent of all deaths occurred in people 65 years of age and over, while today the age at death has been pushed back so that, by 1980, 30 percent of deaths occurred in those over age 80. The greatest declines in age-specific mortality for those 65 and over occurred from 1920 to 1945 and since 1970.

Illness and disability rise with age, and there is some evidence that rates of disability in all age groups may be increasing. Measurement of morbidity and disability is

the area where data are weakest and our needs for data are perhaps greatest. Agreement is needed on the use, limitations, and interpretations of surveys and of data relating to functional status.

In a few years, medical students and physicians will be computer literate. We should plan now for a better utilization of the already available Federal data sets as well as implementation of computerized health care information on individual patients. Some modifications of privacy legislation will probably be necessary in order for physicians to give better care to their patients, and to provide epidemiologic research opportunities in critical areas of public health needs.

Caution is urged in order to maintain credibility in health promotion by avoiding overstatement of knowledge in areas where scientific evidence is weak or lacking. Better utilization and development of epidemiologic and statistical information as well as basic research in chronic diseases are urged to prepare for the year 2025, when there will be some 60 million Americans age 65 and over—about 20 percent of the total population.

AS AN EPIDEMIOLOGIST concerned with health policy, I have the heady sensation that we are riding a great surge forward in human health and longevity in the United States, albeit this surge is not entirely of our creation or even effective maintenance. In the words of leading economist George L. Stolnitz (1), "Demographically, these are the most dramatic times in our history. They are also, almost surely, the most unpredictable and problematic."

"Impressive" and even "awesome" are adjectives that describe the growth of the American population age 65

and older in this century. Between 1900 and 1981, there was a greater than eightfold increase: from approximately 3.1 million people 65 and older in 1900 to 26 million in 1980 (2,3). This was accompanied by a rise in the percentage of those 65 and older from 4.1 to 11.3 percent of the total population. The U.S. Bureau of the Census projects that by the year 2000 the number of persons over age 65 will reach 33.5-36.6 million, accounting for about 13 percent of the total population (3). Within 41 years (by the year 2025), as the post-World War II "baby boom" cohort ages, those 65 and older will